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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM:
Date: May 01, 2008

SUBJECT: Thiencarbazone-Methyl. Report of the Residues of Concern Knowledgebase Subcommittee.

PC Code: 015804
MRID No.: None
Petition No.: 7F7208
Assessment Type: None
TXR No.: None

DP Barcode: DP351125
Registration No.: None
Regulatory Action: None
Reregistration Case No.: None
CAS No.: 317815-83-1

FROM: Edward Scollon, Executive Secretary
Residues of Concern Knowledgebase Subcommittee
Health Effects Division (7509P)

THROUGH: Christine L. Olinger, Co-Chair
Mary Ko Manibusan, Co-Chair
Residues of Concern Knowledgebase Subcommittee
Health Effects Division (7509P)

TO: Risk Assessment Team
Reregistration Branch 3
Health Effects Division (7509P)

The Residues of Concern Knowledgebase Subcommittee (ROCKS) met on March 6, 2008 to discuss the residues of concern for the herbicide thiencarbazone-methyl. Residues of concern were discussed for plants and livestock. On March 27, 2008 the ROCKS committee met with the risk assessment team to discuss drinking water residues of concern.

Team Members:
Peter Savoia, William Donovan, Seyed Tadayon, John Doherty

Received RC 5/6/2008 SH

ROCKS Members Attended:
George Kramer, Marietta Echeverria, Thuy Nguyen, Mary Manibusan, Rick Loranger, Christine Olinger, Leung Cheng, Edward Scollon

Other Attendees:
Amy McKinnon, Joel Paterson (PMRA), Jeff Herndon, Jack Arthur, Paula Deschamp, Kris Barber

Committee Decision:

Table 1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression (Revised).

Matrix		Residues Included In Risk Assessment	Residues Included In Tolerance Expression
Plants	Primary Crop (Corn & Wheat)	Thiencarbazone-methyl *per se*	Thiencarbazone-methyl *per se*
	Rotational Crops	Thiencarbazone-methyl *per se*	Thiencarbazone-methyl + M22
Livestock	Ruminant	Thiencarbazone-methyl *per se*	Thiencarbazone-methyl + M21
	Poultry	Thiencarbazone-methyl *per se*	40 CFR Part 180.6(a)(3)
Drinking Water		Thiencarbazone-methyl *per se*	Not Applicable

Thiencarbazone-methyl =(BYH 18636 parent; 3-thiophenecarboxylic acid, 4-[[[(4,5-dihydro-3-methoxy-4-methyl-5-oxo-1H-1,2,4-triazol-1-yl)carbonyl]amino]sulfonyl]-5-methyl-, methyl ester (CAS); **M21** = 5-methoxy-4-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (IUPAC); **M22** = 2-hexopyranosyl-5-methoxy-4-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (IUPAC)

Rationale:

Plants

Field trials on corn examining pre-emergence, early post-emergence, post-emergence, and late post-emergence applications using the SC 450 and WG 63 formulations were initiated for study. In general, most samples had residues <LOQ, with some positive detections being primarily observed for those treatments which made as post-emergence applications. As such, the maximum concentration of parent, BYH 18636-N-desmethyl (M07) and BYH 18636-MMT –glucoside (M22) measured in each particular sample is summarized in Table 1 for review.

Table 1. Corn Field Trial Residue Summary [1]

Crop	Commodity	Treatment Type[2]	Parent	N-desmethyl (M07)	MMT-glucoside (M22)
Field Corn	Forage	PREV6	<LOQ[3]	<LOQ	0.011
		PPIV6	<LOQ	<LOQ	<LOQ
		V2V6	0.016	<LOQ	0.013
		V2V68	0.037	<LOQ	0.014
	Grain	PREV6	<LOQ	<LOQ	<LOQ
		PPIV6	<LOQ	<LOQ	<LOQ
		V2V6	<LOQ	<LOQ	<LOQ
		V2V68	<LOQ	<LOQ	<LOQ
	Stover	PREV6	0.014	<LOQ	<LOQ
		PPIV6	<LOQ	<LOQ	<LOQ
		V2V6	0.013	<LOQ	<LOQ
		V2V68	0.016	<LOQ	0.012
Sweet Corn	Forage	PREV6	0.012	<LOQ[3]	<LOQ
		PPIV6	0.015	<LOQ	0.014
		V2V6	0.029	<LOQ	0.016
		V2V68	0.160	<LOQ	0.027
	K+CWHR[4]	PREV6	<LOQ	<LOQ	<LOQ
		PPIV6	<LOQ	<LOQ	<LOQ
		V2V6	<LOQ	<LOQ	<LOQ
		V2V68	<LOQ	<LOQ	<LOQ
	Stover	PREV6	<LOQ	<LOQ	<LOQ
		PPIV6	0.023	<LOQ	0.023
		V2V6	0.024	<LOQ	0.027
		V2V68	0.042	<LOQ	<LOQ
Pop Corn	Grain	PREV6	<LOQ	<LOQ	<LOQ
		PPIV6	<LOQ	<LOQ	<LOQ
		V2V6	<LOQ	<LOQ	<LOQ
		V2V68	<LOQ	<LOQ	<LOQ
	Stover	PREV6	<LOQ	<LOQ	<LOQ
		PPIV6	<LOQ	<LOQ	<LOQ
		V2V6	<LOQ	<LOQ	<LOQ
		V2V68	<LOQ	<LOQ	<LOQ

[1] All maxima reported occurred in separate samples.

[2] For the corn field trials, the PREV6 plot received a pre-plant application of the 1.88 lb/gal FlC formulation and a post-emergence application of the 21% WDG formulation at target V6 growth stage; the PPIV6 plot received a pre-plant incorporated application of the 1.88 lb/gal FlC formulation and a post-emergence application of the 21% WDG formulation at target V6 growth stage; the V2V6 plot received a post-emergence application of the 1.88 lb/gal FlC formulation at target V2 growth stage and a post-emergence application of the 21% WDG formulation at target V6 growth stage; and the V2V68 plot

received a post-emergence application of the 1.88 lb/gal FlC formulation at target V2 growth stage and two post-emergence applications of the 21% WDG formulation at Target V6 and V8 growth stages.
[3] 0.010 ppm Limit of Quantitation.
[4] Kernel plus Cob with Husk Removed

In regard to the field trials performed on wheat, a post-emergence treatment using the OD 70 formulation was made with all commodities being harvested at maturity for testing. Residue levels for these samples were generally <LOQ with few maximum levels observed to be nominally greater than this concentration. For this evaluation, the maximum concentration of parent, BYH 18636-N-desmethyl (M07) and BYH 18636-MMT–glucoside (M22) measured in each particular sample is summarized in Table 2 for review.

Table 2. Wheat Field Trial Residue Summary.[1]

Crop	Commodity	Days After Last Treatment (DALT)	Parent	N-desmethyl (M07)	MMT-glucoside (M22)
Wheat	Forage	≈ 6	0.050	0.040	<LOQ[2]
	Hay	≈ 30	<LOQ	<LOQ	<LOQ
	Grain	≈ 60	<LOQ	<LOQ	<LOQ
	Straw	≈ 60	<LOQ	<LOQ	<LOQ

[1] All maxima reported occurred in separate samples.
[2] 0.010 ppm Limit of Quantitation.

Based upon the primary crop field trial results presented above, it would be appropriate to designate parent thiencarbazone-methyl *per se* as the residue of concern for all corn and wheat commodities. This conclusion is drawn from the fact that the highest maximum residue level most frequently occurring among all three compounds was generally parent BYH 18636. As a result, the parent compound will in all probability serve as the best indicator of potential misuse in those samples likely having residues >LOQ.

In the field rotational crop studies performed using soybeans and wheat, very low residues were found in these commodities harvested at maturity for testing. Several plant-back intervals (PBIs) were evaluated for these commodities following application with the WG 63 formulation. Subsequently, the maximum concentration of parent, BYH 18636-N-desmethyl (M07) and BYH 18636-MMT–glucoside (M22) measured in each particular sample is summarized in Table 3 for review.

BYH 18636-MMT–glucoside (M22) is the glucosidation product of the BYH 18636-MMT (M21) cleavage fragment. Resemblance to the parent is minimal and DEREK analysis did not indicate any alerts. BYH 18636-N-desmethyl (M07) is a single demethylation product and therefore very structurally similar to the parent. However, it was not found to be toxic to rats fed 12000 ppm over 90 days. Therefore, ROCKS determined the metabolites BYH 18636-MMT–glucoside (M22) and BYH 18636-N-desmethyl (M07) were not a toxicological concern.

Table 3. Rotational Crop Field Trial Residue Summary.[1]				
Soybean				
Plant Back Interval (PBI)	Commodity	Parent	N-desmethyl (M07)	MMT-glucoside (M22)
2 Months	Forage	<LOQ[2]	<LOQ	0.021
	Hay	<LOQ	<LOQ	0.073
	Seed	<LOQ	<LOQ	<LOQ
9 Months	Forage	<LOQ	<LOQ	<LOQ
	Hay	<LOQ	<LOQ	0.020
	Seed	<LOQ	<LOQ	<LOQ
12 Months	Forage	<LOQ	<LOQ	<LOQ
	Hay	<LOQ	<LOQ	0.017
	Seed	<LOQ	<LOQ	<LOQ
Wheat				
3 Months	Forage	<LOQ	<LOQ	<LOQ
	Hay	<LOQ	<LOQ	<LOQ
	Grain	<LOQ	<LOQ	<LOQ
	Straw	<LOQ	<LOQ	<LOQ

[1] All maxima reported occurred in separate samples.
[2] 0.010 ppm Limit of Quantitation.

Review of the rotational crop field trial results shows that positive detections were incurred for the metabolite BYH 18636-MMT-glucoside (M22). Following the PBIs specified on the WG 63 product label, 3 months for wheat and 2 months for soybean, rotational crop tolerances should be established for those commodities which yielded residues > LOQ (soybean forage & hay). As such, the rotational crop tolerance expression will be parent along with its BYH 18636-MMT-glucoside (M22) metabolite expressed as thiencarbazone-methyl. For risk assessment however, the residue of concern will be parent thiencarbazone-methyl only since its metabolite has far less toxicity.

Livestock

The major residues observed in the ruminant and poultry metabolism studies were BYH 18636 parent, BYH 18636-MMT (M21), and methyl carbamate (M23). In the hen study, thiencarbazone-methyl was found in eggs (83.2% TRR) and BYH 18636-MMT (M21) was found in eggs (69.6% TRR), muscle (55.1% TRR) and fat (49.3% TRR). BYH 18636-MMT (M21) and methyl carbamate (M23) were found in all tissue matrixes examined in the lactating goat study, up to 49.4% in the kidney and 43.9% TRR in the fat, respectively. No toxicological data were available for BYH 18636-MMT (M21), however, the metabolite is structurally dissimilar from the thiencarbazone-methyl and DEREK analysis did not indicate any alerts. Due to the low toxicity and relative abundance of BYH 18636-MMT (M21) in tissue, it can serve as an indicator of misuse. Methyl carbamate (M23) was not found in the required bovine feeding study. Therefore, ROCKS recommends the residues of concern for livestock risk assessment and tolerance

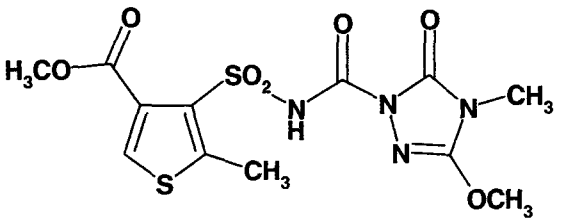
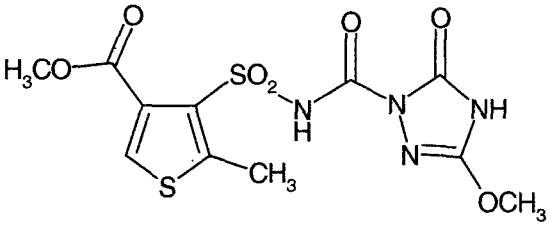
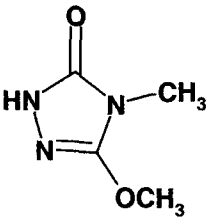
expression are thiencarbazone-methyl and thiencarbazone-methyl plus BYH 18636-MMT (M21) as an indicator of abuse.

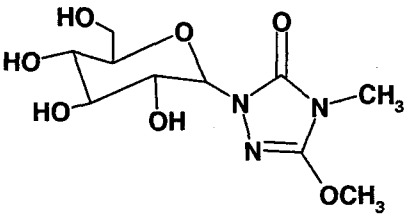
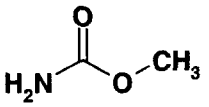
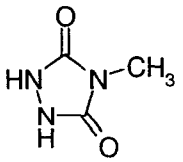
Water

Aerobic soil metabolism and anaerobic aquatic metabolism appear to be the major routes of degradation for thiencarbazone-methyl with half-lives of 3.2 days to 43 days and 7.6 days, respectively. Thiencarbazone-methyl is stable to both aqueous and soil photolysis. BYH 18636 parent degrades slowly via hydrolysis with half lives of 49.5 days at pH 4; 148 days at pH 7; and 154 days at pH 9. Thiencarbazone-methyl degrades slowly via anaerobic soil metabolism with a half-life of 108 days. Thiencarbazone-methyl degrades moderately under aerobic aquatic conditions with half-lives of 18.1 to 28.2 days.

Major terminal metabolites including BYH 18636-carboxylic acid (M01), BYH 18636-sulfonamide-carboxylic acid (M03), and BYH 18636-MMT (M21) were found in soil, aquatic and field dissipation studies. BYH 18636-carboxylic acid (M01) and BYH 18636-MMT (M21) were found in aquatic (aerobic/anaerobic) and aquatic (aerobic) environments, respectively. BYH 18636-sulfonamide (M15), a transitory metabolite, was found in, soil (aerobic). BYH 18636-dicarboxy-sulfonamide (M25) and BYH-NMT were found in an/aerobic aquatic environments and anaerobic aquatic environments, respectively. None of these metabolites were considered to be of concern for the toxicological reasons discussed in the Plant and Livestock sections in addition to Appendix 2. Therefore, ROCKS recommends the residue of concern for the drinking water risk assessment and tolerance expression is thiencarbazone-methyl.

Table of Metabolite Structures and Names

Appendix 1. Summary of Chemical Names and Structures of Thiencarbazone-Methyl and Metabolites.			
	Report name **Structure** **IUPAC name** **CAS name** **[CAS number]**	**Molecular formula** **molar mass** **Other names / codes**	**Occurrence**
a.s.	**BYH 18636** (parent substance) **thiencarbazone-methyl** (common name)  methyl 4-[(4,5-dihydro-3-methoxy-4-methyl-5-oxo-1H-1,2,4-triazol-1-yl)carboxamidosulfonyl]-5-methylthiophene-3-carboxylate (IUPAC) 3-thiophenecarboxylic acid, 4-[[[(4,5-dihydro-3-methoxy-4-methyl-5-oxo-1H-1,2,4-triazol-1-yl)carbonyl]amino]sulfonyl]-5-methyl-, methyl ester (CAS) [CAS No.: 317815-83-1]	$C_{12}H_{14}N_4O_7S_2$ 390.4 g/mol parent compound thiencarbazone-methyl AE 1162464	All matrices
M07	**BYH 18636-N-desmethyl**  methyl 4-({[(3-methoxy-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)carbonyl]amino}sulfonyl)-5-methylthiophene-3-carboxylate (IUPAC)	$C_{11}H_{12}N_4O_7S_2$ 376.37 g/mol AE 1417257 GSE 28223	Plant Animal (hen, goat) Not in the rat but toxicologically tested and of no concern
M21	**BYH 18636-MMT**  5-methoxy-4-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (IUPAC)	$C_4H_7N_3O_2$ 129.1 g/mol AE 1277106 GSE12201	Soil Water Hydrolysis study Plant Rat (0.47 % of dose but 0.2 % was an impurity in the administration suspension) Animal (hen, goat)

Appendix 1. Summary of Chemical Names and Structures of Thiencarbazone-Methyl and Metabolites.			
	Report name **Structure** **IUPAC name** **CAS name** **[CAS number]**	**Molecular formula** **molar mass** **Other names / codes**	**Occurrence**
M22	**BYH 18636-MMT-glucoside**  2-hexopyranosyl-5-methoxy-4-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one (IUPAC)	$C_{10}H_7N_3O_2$ 291.3 g/mol	Plant Animal (aglycon of this conjugate)
M23	**methyl carbamate** **(BYH 18636-methyl carbamate)**  methyl carbamate (IUPAC) methylcarbamate (CAS) [CAS No.: 598-55-0]	$C_2H_5NO_2$ 75.1 g/mol methylurethane Carbamic acid methyl ester	Animal (hen, goat, not in ruminant feeding study) Rat
	BYH 19636-NMT  4-Methyl-1,2,4-triazolidine-3,5-dione [CAS #-16312-79-1]	 N-methyltriazolinone	Anaerobic Aquatic Metabolism (Major)

Appendix 2. **ROCKS MEMORANDUM**

To: ROCKS Committee
From: Mary Manibusan, ROCKS Co-Chair
Senior Toxicologist
Date: March 28, 2008
Re: Thiencarbazone methyl (TCM) Toxicity Rationale for Metabolites of Exposure Concern

THIENCARBAZONE METHYL

Background: Thiencarbazone Methyl (TCM) is a sulfonamide related chemical being developed as a pesticide. The registration of this new active ingredient is a joint work-share effort being carried out in part with PMRA Canada and PSD United Kingdom as a trilateral review.

Thiencarbazone Rodent Mode of Action:

Sulfonamides and related chemicals are known to have poor solubility in aqueous solutions such as urine. When ingested orally, they are rapidly absorbed and excreted primarily in the urine or in the urine and feces, as is the case for TCM. In the urinary tract, depending on solubility and various other factors affecting urinary chemical composition, urinary crystals are readily formed and in some species, also calculi. In rodents, as in the case for TCM, crystals and calculi readily form.

In the case for TCM, it appears that the urinary tract solids are formed primarily of the parent chemical itself rather than metabolites or from normal constituents of the urine. It is clear that it is not the chemical that is toxic, but rather, it is the urinary solids formed from the chemical. Urinary tract calculi represent a high dose phenomenon dependent on basic physical chemical properties of the solubility products of the chemical involved. This is the clearest example of a threshold phenomenon for carcinogenesis and is similar to that described for cyprosulfamide; the formation of stones at high doses leads to local irritation, degeneration, proliferative changes and hyperplasia; if exposure and effects are sustained, these proliferative responses could progress to tumor formation.

Rat Metabolic Pathway:

Metabolism of Thiencarbazone-methyl was evaluated using parent chemical C^{14} labeled within the dihydrotriazole or thiophene moieties. Thiencarbazone-methyl was found to be rapidly absorbed within 24 hours following oral administration. In all dose groups, plasma Cmax was attained within 1 hour of dosing. Absorption following oral administration was found to be moderate and is calculated to range between 48-55%.

The distribution of radioactivity following dosing was rapid and relatively even, however slightly higher levels or radioactivity were found in the lungs and fat or in the adrenals and thyroids. Total tissue residues at 14 hours following dosing were <1% of the administered dose and do not indicate that thiencarbazone methyl has the potential to bioaccumulate. Thiencarbazone-methyl and its metabolites were rapidly and extensively excreted following oral administration.

The metabolism of thiencarbazone-methyl was found to be limited with 91-92% of the administered dose excreted as unchanged parent compound. It is postulated that metabolism of thiencarbazone-methyl proceeds by the initial hydrolysis of the urea group, releasing the thiophene-sulphonamide moiety. Hydrolysis of the methyl ester releases the sulphonamide-carboxylic acid that is subsequently cyclized to the thiensaccharine, following the formation of an intramolecular sulphonamide bond. A second metabolic path starts with the hydrolysis of thiencarbazone-methyl to form the MMT derivative. Demethylation of the MMT derivative forms the MMT derivative with subsequent cleavage of the triazolinone moiety to form methyl carbamate.

Structure Activity Analysis and Toxicity Conclusions on the Metabolites of Concern:

M01: M01 is a carboxylic acid metabolite of TCM and in the absence of data would be expected to be of equal or lesser toxicity than the parent compound. A 90-day oral rat study indicates M01 is significantly less toxic than the parent as no adverse effects were noted in the highest dose test at 15000 ppm in both sexes.

M03: M03 is similar in structure to M15, but in lieu of the ester substituent group at the 3 position of the thiophene ring, there is a carboxylic acid group. M03, the hydrolyzed carboxylic acid form of M15, is not expected to exhibit a different toxicity profile than M15 (see M15), but may be less toxic due to higher excretion.

M07: M07 is a N-desmethyl metabolite of TCM and the only structural difference is the lack of a methyl group off the dihydrotriazole ring. In the absence of data, this demethylation would not be expected to contribute to a different toxicity. A 28-day oral rat study was conducted that shows a lack of toxicity at the highest dose tested of 12,000 ppm in both sexes.

M15: M15 is a cleaved sulfonamide metabolite of TCM, retaining only the thiophene ring and aminosulfonyl group at the 4 position. A 28-day oral rat study has been conducted showing no effects at the highest dose tested of 10,000 ppm in both sexes. M15 was also found to be not mutagenic in the Ames assay.

M21: M21 is a cleavage product retaining only the dihydrotriazole ring portion (1,2,4 triazol-3-one) of TCM. The Derek analysis did not report any structural alerts to indicate a different toxicity profile from the parent compound. The expectation based on the MOA is that any metabolite not retaining the sulfonamide linkage would be less toxic based on enhanced excretion.

M22: M22 is similar to M21, but with the additional glucoside substituent group. A similar Derek toxicity prediction was produced with no known structural alerts triggered, but again the expectation based on the MOA is that this metabolite would be less toxic based on enhanced excretion.

M25: M25 is a dicarboxy-sulfonamide, which is essentially similar to M15 but with a carboxylic acid substituted for the ester group, and an additional carboxylic acid group at the 4 position of the ring. These differences are not expected to elicit a different level of toxicity compared to M15. M15 has empirical animal data indicating no adverse effects at 10,000 ppm and negative for any mutagenic response.

Derek Reports for TCM Metabolites

F:\QSAR\Thiencarbazone-Methyl-M22.rtf

Derek for Windows Report

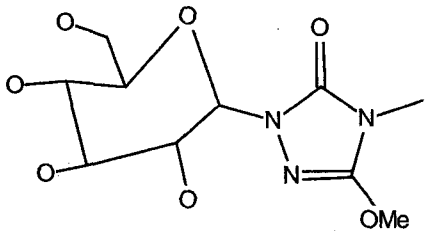
User name:	Mary Manibusan
Date created:	Tuesday, March 04, 2008
Program version:	Derek for Windows_10.0.2
Filename of knowledge base:	C:\Program Files\Lhasa Ltd\LPS 10.0.2\DfW10.mdb
Knowledge base version:	DfW10.0.0_25_07_2007
Knowledge base last modified date:	Thursday, July 26, 2007
Testing a single alert:	Off
Species:	bacterium
	mammal
Superendpoints:	Carcinogenicity
	Chromosome damage
	Genotoxicity
	Hepatotoxicity
	HERG channel inhibition
	Irritation
	Miscellaneous endpoints
	Mutagenicity
	Reproductive toxicity
	Respiratory sensitisation
	Skin sensitisation
	Thyroid toxicity
Perceive tautomers:	On
Hydrogen options:	Perceive implicit and explicit hydrogens
Autosave results (DRK file):	Off
Autosave results directory:	Not applicable
Name field:	atrazine

Derek for Windows Report

Compound name:	F:\QSAR\Thiencarbazone-Methyl-M22.mol
Relative molecular mass:	291.26 Calculated by LPS
Exact molecular mass:	291.10665 Calculated by LPS
Log Kp:	-5.16 cm/h [for Kp] Obtained from External Data Source
Molecular weight =	291.26

Log P value used in Log Kp calculation = -0.934
Log P: -0.934 Obtained from External Data Source

Submitted compound:



List of alerts found:

448 Hydrazine or precursor. Skin sensitisation. Number of matches = 1

LHASA PREDICTIONS

Photoallergenicity

mammal - Reasoning

Photoallergenicity in mammal is DOUBTED
Rule 246: If [Log Kp < -5] is [certain] then [Photoallergenicity] is [Species dependent variable 6]
[Log Kp < -5] is [CERTAIN]
Log Kp is -5.16 cm/h [for Kp] Obtained from External Data Source
[Species dependent variable 6] is [DOUBTED]
Rule 223: If [species human] is [certain] then [Species dependent variable 6] is [improbable]
[species human] is [PLAUSIBLE]

Rules for mammal and Photoallergenicity

Rule name: Rule 223
Rule 223: If [species human] is [certain] then [Species dependent variable 6] is [improbable]
Comments: In the human the variable "Species dependent variable 6" is improbable.
References:
(No References)

Rule name: Rule 246
Rule 246: If [Log Kp < -5] is [certain] then [Photoallergenicity] is [Species dependent variable 6]
Comments: If the chemical has a Log Kp value of less than -5 cm/h then photoallergenicity is considered improbable in humans, impossible in bacteria and open in all other species. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 6".A Log Kp value of less than -5 cm/h is considered to represent low

penetration of the skin [Howes et al].Human Log Kp values are calculated from the molecular weight and Log P values of a chemical using the Potts and Guy equation [Potts and Guy]. This equation is derived from a data set of about ninety chemicals with a molecular weight range of 18 to >750 and a Log P range of -3 to +6. Less confidence should be placed in Log Kp values calculated from this equation where chemicals have a molecular weight and/or a Log P value outside of these training set ranges.
References:

Title: Predicting skin permeability.
Author: Potts RO and Guy RH.
Source: Pharmaceutical Research, 1992, 9, 663-669.

Title: Methods for assessing percutaneous absorption: the report and recommendations of ECVAM workshop 13.
Author: Howes D, Guy R, Hadgraft J, Heylings J, Hoeck U, Kemper F, Maibach H, Marty JP, Merk H, Parra J, Rekkas D, Rondelli I, Schaefer H, Tauber U and Verbiese N.
Source: Alternatives to Laboratory Animals, 1996, 24, 81-106.

Rule name: Rule 247
Rule 247: If [species bacterium] is [certain] then [Species dependent variable 6] is [impossible]
Comments: In bacteria the variable "Species dependent variable 6" is impossible.
References:
(No References)

Skin sensitisation

mammal - Reasoning

Skin sensitisation in mammal is EQUIVOCAL
Rule 58: If [Skin sensitisation alert] is [certain] then [Skin sensitisation] is [Species dependent variable 22]
[Skin sensitisation alert] is [CERTAIN]
[Species dependent variable 22] is [PLAUSIBLE]
Rule 243: If [species mammal] is [certain] then [Species dependent variable 22] is [plausible]
[species mammal] is [CERTAIN]
Rule 248: If [Log Kp < -5] is [certain] then [Skin sensitisation] is [Species dependent variable 6]
[Log Kp < -5] is [CERTAIN]
Log Kp is -5.16 cm/h [for Kp] Obtained from External Data Source
[Species dependent variable 6] is [DOUBTED]
Rule 223: If [species human] is [certain] then [Species dependent variable 6] is [improbable]
[species human] is [PLAUSIBLE]

Rules for mammal and Skin sensitisation

Rule name: Rule 223
Rule 223: If [species human] is [certain] then [Species dependent variable 6] is [improbable]
Comments: In the human the variable "Species dependent variable 6" is improbable.
References:
(No References)

Rule name: Rule 242
Rule 242: If [species bacterium] is [certain] then [Species dependent variable 22] is [impossible]
Comments: In bacteria the variable "Species dependent variable 22" is impossible.
References:
(No References)

Rule name: Rule 243
Rule 243: If [species mammal] is [certain] then [Species dependent variable 22] is [plausible]

Comments: In mammals the variable "Species dependent variable 22" is plausible.
References:
(No References)

Rule name: Rule 247
Rule 247: If [species bacterium] is [certain] then [Species dependent variable 6] is [impossible]
Comments: In bacteria the variable "Species dependent variable 6" is impossible.
References:
(No References)

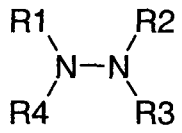
Rule name: Rule 248
Rule 248: If [Log Kp < -5] is [certain] then [Skin sensitisation] is [Species dependent variable 6]
Comments: If the chemical has a Log Kp value of less than -5 cm/h then skin sensitisation is considered improbable in humans, impossible in bacteria and open in all other species. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 6".A Log Kp value of less than -5 cm/h is considered to represent low penetration of the skin [Howes et al].Human Log Kp values are calculated from the molecular weight and Log P values of a chemical using the Potts and Guy equation [Potts and Guy]. This equation is derived from a data set of about ninety chemicals with a molecular weight range of 18 to >750 and a Log P range of -3 to +6. Less confidence should be placed in Log Kp values calculated from this equation where chemicals have a molecular weight and/or a Log P value outside of these training set ranges.
References:

Title: Predicting skin permeability.
Author: Potts RO and Guy RH.
Source: Pharmaceutical Research, 1992, 9, 663-669.

Title: Methods for assessing percutaneous absorption: the report and recommendations of ECVAM workshop 13.
Author: Howes D, Guy R, Hadgraft J, Heylings J, Hoeck U, Kemper F, Maibach H, Marty JP, Merk H, Parra J, Rekkas D, Rondelli I, Schaefer H, Tauber U and Verbiese N.
Source: Alternatives to Laboratory Animals, 1996, 24, 81-106.

Rule name: Rule 58
Rule 58: If [Skin sensitisation alert] is [certain] then [Skin sensitisation] is [Species dependent variable 22]
Comments: If a chemical contains an alert for skin sensitisation then it is considered plausible that the chemical will cause skin sensitisation in mammals and impossible in bacteria. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 22".
References:
(No References)

Alert overview: 448 Hydrazine or precursor



R1-R4 = C, H

Comments:
The alert also includes coverage for hydrazone precursors of hydrazines.

The presence of a skin sensitisation structural alert within a molecule indicates the molecule has the potential to cause skin sensitisation. Whether or not the molecule will be a skin sensitiser will also depend upon its percutaneous absorption. Generally, small lipophilic molecules are more readily absorbed into the skin and are therefore more likely to cause sensitisation.

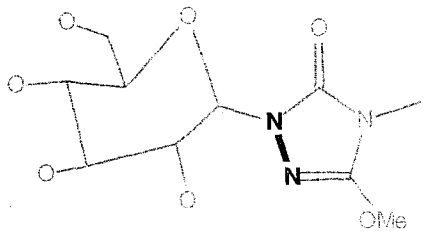
References:

Title: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung.
Author: Kayser D and Schlede E (editors).
Source: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung, Kayser D and Schlede E (editors), Urban & Vogel Medien und Medizin Verlagsgesellschaft, Munich, 2001.

Title: Guinea pig maximization test.
Author: Wahlberg JE and Boman A.
Source: Current Problems in Dermatology, 1985, 14, 59-106.

Title: Irritants and sensitisers.
Author: Rycroft RJG and Wilkinson JD.
Source: Textbook of Dermatology, 5th edition, volume 1, Champion RH, Burton JL and Ebling FJG (editors), Blackwell, Oxford, 1991, 717-754.

Locations:



Examples: (448 Hydrazine or precursor)

Example 1. hydrazine
CAS Number: 302-01-2

Test Data: (hydrazine)

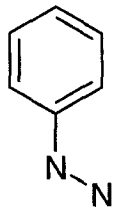
1.
Species: various
Assay: various
Result: BgVV category A

References:

Title: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung.
Author: Kayser D and Schlede E (editors).

Source: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung, Kayser D and Schlede E (editors), Urban & Vogel Medien und Medizin Verlagsgesellschaft, Munich, 2001.

Example 2. phenylhydrazine
CAS Number: 100-63-0



Test Data: (phenylhydrazine)

1.
Species: various
Assay: various
Result: BgVV category A

References:

Title: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung.
Author: Kayser D and Schlede E (editors).
Source: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung, Kayser D and Schlede E (editors), Urban & Vogel Medien und Medizin Verlagsgesellschaft, Munich, 2001.

Custom Examples: (448 Hydrazine or precursor)

(No examples)

F:\QSAR\Thiencarbazone-Methyl-M21.rtf

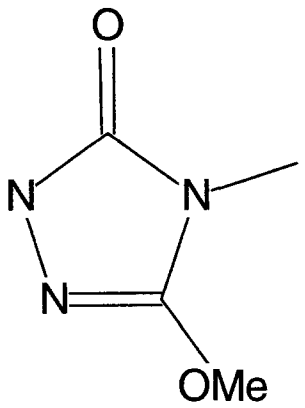
Derek for Windows Report

User name:	Mary Manibusan
Date created:	Tuesday, March 04, 2008
Program version:	Derek for Windows_10.0.2
Filename of knowledge base:	C:\Program Files\Lhasa Ltd\LPS 10.0.2\DfW10.mdb
Knowledge base version:	DfW10.0.0_25_07_2007
Knowledge base last modified date:	Thursday, July 26, 2007
Testing a single alert:	Off
Species:	bacterium
	mammal
Superendpoints:	Carcinogenicity
	Chromosome damage
	Genotoxicity
	Hepatotoxicity
	HERG channel inhibition
	Irritation
	Miscellaneous endpoints
	Mutagenicity
	Reproductive toxicity
	Respiratory sensitisation
	Skin sensitisation
	Thyroid toxicity
Perceive tautomers:	On
Hydrogen options:	Perceive implicit and explicit hydrogens
Autosave results (DRK file):	Off
Autosave results directory:	Not applicable
Name field:	atrazine

Derek for Windows Report

Compound name:	F:\QSAR\Thiencarbazone-Methyl-M21.mol
Relative molecular mass:	129.119 Calculated by LPS
Exact molecular mass:	129.05383 Calculated by LPS
Log Kp:	-3.848 cm/h [for Kp] Obtained from External Data Source
Molecular weight =	129.119
Log P value used in Log Kp calculation =	-0.48
Log P:	-0.48 Obtained from External Data Source

Submitted compound:



List of alerts found:

448 Hydrazine or precursor. Skin sensitisation. Number of matches =

LHASA PREDICTIONS

Skin sensitisation

mammal - Reasoning

Skin sensitisation in mammal is PLAUSIBLE

Rule 58: If [Skin sensitisation alert] is [certain] then [Skin sensitisation] is [Species dependent variable 22]

[Skin sensitisation alert] is [CERTAIN]

[Species dependent variable 22] is [PLAUSIBLE]

Rule 243: If [species mammal] is [certain] then [Species dependent variable 22] is [plausible]

[species mammal] is [CERTAIN]

Rules for mammal and Skin sensitisation

Rule name: Rule 242

Rule 242: If [species bacterium] is [certain] then [Species dependent variable 22] is [impossible]
Comments: In bacteria the variable "Species dependent variable 22" is impossible.
References:
(No References)

Rule name: Rule 243

Rule 243: If [species mammal] is [certain] then [Species dependent variable 22] is [plausible]
Comments: In mammals the variable "Species dependent variable 22" is plausible.
References:
(No References)

Rule name: Rule 58

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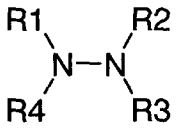
Comments: If a chemical contains an alert for skin sensitisation then it is considered plausible that the chemical will cause skin sensitisation in mammals and impossible in bacteria. The variation in rule outcome with species is achieved via use of the variable "Species dependent variable 22".
References:
(No References)

Alert overview: 448 Hydrazine or precursor



R1-R4 = C, H

Comments:
The alert also includes coverage for hydrazone precursors of hydrazines.

The presence of a skin sensitisation structural alert within a molecule indicates the molecule has the potential to cause skin sensitisation. Whether or not the molecule will be a skin sensitiser will also depend upon its percutaneous absorption. Generally, small lipophilic molecules are more readily absorbed into the skin and are therefore more likely to cause sensitisation.

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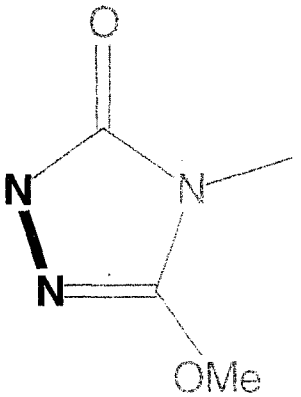
Author: Kayser D and Schlede E (editors).
Source: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung, Kayser D and Schlede E (editors), Urban & Vogel Medien und Medizin Verlagsgesellschaft, Munich, 2001.

Title: *Guinea pig maximization test.*
Author: Wahlberg JE and Boman A.
Source: Current Problems in Dermatology, 1985, 14, 59-106.

Title: Irritants and sensitisers.
Author: Rycroft RJG and Wilkinson JD.
Source: Textbook of Dermatology, 5th edition, volume 1, Champion RH, Burton JL and Ebling FJG (editors), Blackwell, Oxford, 1991, 717-754.

Locations:



Examples: (448 Hydrazine or precursor)

Example 1. hydrazine
CAS Number: 302-01-2

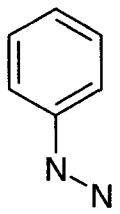
Test Data: (hydrazine)

1.
Species: various
Assay: various
Result: BgVV category A

References:

Title: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung.
Author: Kayser D and Schlede E (editors).
Source: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung, Kayser D and Schlede E (editors), Urban & Vogel Medien und Medizin Verlagsgesellschaft, Munich, 2001.

Example 2. phenylhydrazine
CAS Number: 100-63-0



Test Data: (phenylhydrazine)

1.
Species: various
Assay: various
Result: BgVV category A

References:

Title: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung.
Author: Kayser D and Schlede E (editors).
Source: Chemikalien und Kontaktallergie: Eine Bewertende Zusammenstellung, Kayser D and Schlede E (editors), Urban & Vogel Medien und Medizin Verlagsgesellschaft, Munich, 2001.

Custom Examples: (448 Hydrazine or precursor)

(No examples)

13544

R158982

Chemical Name: Thiencarbazone-methyl

PC Code: 015804
HED File Code: 11000 Chemistry Reviews
Memo Date: 5/1/2008
File ID: DPD351125
Accession #: 000-00-0125

HED Records Reference Center
7/2/2008